REMARKS

Favorable reconsideration of the application as amended is respectfully requested.

I. STATUS OF THE CLAIMS

Claims 1, 3-4, 7, 9-13, and 15-17 have been amended. Claims 5-6, 14, and 18-22 have been canceled. Claims 13 and 15-17 are withdrawn as non-elected.

No new matter has been added. Support for amendment to claim 1 can be found in claim 1 as filed and in the specification on:

- page 5, lines 1-2 (of the PCT publication WO 2004/060407): "in the context of the invention, we have developed calcium phosphate ceramics and powders capable of tranfecting cells both in vivo and in vitro";
- page 5, lines 4-8 (of the PCT publication WO 2004/060407): "the chemical composition of these ceramics may vary because orthophosphoric several acid salts enter into their composition, in particular...hydroxyapatite..."
- page 10, lines 15-16 (of the PCT publication WO 2004/060407): "the ceramics may be porous or dense ceramics"
- page 11, lines 6-7 (of the PCT publication WO 2004/060407): "these products are particularly efficient for the transfection of cells in vitro and in vivo"

Support for the amendment to claim 4 can be found in claim 3 as filed.

Support for the amendment to claim 15 can be found in the specification as filed (page 14, in the table of the PCT publication WO 2004/060407).

Claims 5-6, 14, and 18-22 have been cancelled.

II. OBJECTION TO THE CLAIMS

The objection to claims 13-14 has been obviated by amendment of claim 13 and cancelation of claim 14. Accordingly, the objection is moot.

III. PRELIMINARY REMARKS REGARDING THE INVENTION

The invention as presently claimed concerns a method for producing dense hydroxyapatite ceramics containing DNA molecules attached to their surface and dense hydroxyapatite ceramics, having particular physicochemical properties, said ceramics being capable of tranfecting cells *in vivo* and *in vitro*. The invention also concerns the use of these dense hydroxyapatite ceramics for cellular transfection.

The dense hydroxyapatite ceramics obtained by the method of the invention, and the dense hydroxyapatite ceramics having particular physicochemical properties according to the invention, have in particular the following advantages, which contribute to and advance the state of the art:

- they allow to obtain a good cellular transfection efficiency *in vitro* but also *in vivo*. On the contrary, certain cellular transfection techniques are limited to an *in vitro* application. For example, the calcium phosphate coprecipitates used for several years for efficiently transfecting cells *in vitro* are unusable *in vivo*;
- they do not present toxicity toward cells. Indeed, since DNA is fixed to the surface of ceramic, its release does not require the ceramic degradation; this avoids the modification of the extracellular medium, which can be toxic and lead to cells death. On the contrary, some particles which encapsulate DNA require their degradation to release DNA; so these particles can be toxic and lead to cells death, especially when their degradation occurs in a closed medium like a cell culture medium;
- they allow to obtain cellular transfection prolonged in time. Indeed, the Inventors have surprisingly showed that although ceramics according to the invention allow the fast release of DNA in the medium, they allow cellular transfection prolonged in time. Indeed, as indicated in example 3.1. of the present application, the Inventors have observed, in particular *in vivo*, a significant increase of the percentage of transfected cells, from 4 to 30 days after transfection;

- they allow efficient transfection of cells located near ceramics as well as cells located relatively far from ceramics. This effect is particularly unexpected, given the relatively important size of ceramics according to the invention, which migrate with difficulty in the intercellular space. This property of the ceramic according to the invention is particularly interesting not only for *in vitro* but also for *in vivo* applications, in particular for therapeutic application;
- They allow efficient cellular transfection in the absence of phagocytosis. Indeed, the dense hydroxyapatite ceramics according to the invention are too voluminous to be phagocyted by cells. The absence of phagocytosis allows avoiding the activation of the immune system; this is particularly interesting for *in vivo* application, in particular for therapeutic application.

IV. NONOBVIOUSNESS

Claims 1-9 and 12 and 21-22 stand rejected under 35 U.S.C. 103(a) as obvious over WO 02-085330 (Troczynsky) alone.

Applicants respectfully traverse.

Troczynsky describes microspheres and coatings capable to encapsulate any type of drug or protein, which can be dispersed in organic liquid or water (page 7, lines 5-7). This drug can be DNA molecule (page 10, line 26). These particles are described to be useful for therapeutic application, in particular for gene therapy application.

Contrary to the dense hydroxyapatite ceramics of the present invention, particles described in Troczynsky (in particular in the example 3) are obtained by precipitation. Crystals constituted *in situ* and not linked by grain boundaries constitute the particles of Troczynsky.

The particles disclosed in Troczynsky are consequently less dense and less stable than the dense hydroxyapatite ceramic of the present invention. Particles obtained by precipitation are more soluble than the dense hydroxyapatite ceramic according to the invention; this modifies considerably their behaviour in the body, in particular their degradation, which is much faster

than the degradation of the ceramics of the invention. The inflammatory response provoked by the particles of Troczynsky is thus also much faster.

A. Troczynsky Omits Numerous Claim Limitations

"All words in a claim must be considered in judging the patentability of that claim against the prior art." M.P.E.P. § 2143.03, quoting In re Wilson, 424 F.2d 1382, 1385 (C.C.P.A. 1970).

Here, the claims as amended are nonobvious because Troczynsky fails to satisfy several limitations of the claims as amended. Troczynsky does not disclose a method for producing dense hydroxyapapite ceramics nor such ceramics with DNA molecules attached to their surface and even less a method for producing ceramics capable of transfecting cells *in vivo* and *in vitro*.

In particular, the subject-matter of amended claim 1 differs from the teaching of Troczynsky, by the fact that the process according to the invention:

- forms dense hydroxyapatite ceramics;
- includes step a) hydratation of the dense hydroxyapatite ceramic in a phosphate buffer solution not saturated with calcium and phosphate;
- includes step b) immersion of the product obtain in step a) in a phosphate buffer solution not saturated with calcium and phosphate containing a single or double stranded DNA for periods varying from a few minutes to several hours;
- attaches DNA molecules to the surface of dense hydroxyapatite ceramic;
- yields dense hydroxyapatite ceramics capable of transfecting cells both *in vivo* and *in vitro*.

The technical effect conferred by these differences is the production of ceramics capable of transfecting cells both *in vivo* and *in vitro* without toxicity and without phagocytosis by allowing efficient transfection prolonged in time of cells located near ceramic but also relatively far from them.

This effect is clearly demonstrated in the examples of the present application, in particular in Example 3.1. (Table page 16 of the PCT application WO 2004/060407), 3.2.3 (pages 17-18 of the PCT application WO 2004/060407) and 3.2.4.

B. Unexpected Results Establish Nonobviousness

Applicants have surprisingly shown that although the dense hydroxyapatite ceramics according to the invention allow fast release of DNA in medium (because DNA is attached to the ceramic surface), these ceramics allow cellular transfection prolonged in time with a transfection efficiency, which increases in time. As indicated in Example 3.1. of the present application, Applicants have observed, in particular *in vivo*, a significant increase of the percentage of transfected cells, from 4 to 30 days after transfection.

Troczynsky does not suggest that *in vivo* or *in vitro* transfection, without toxicity, without phagocytosis, prolonged in time, of cells located near particles as well as far from them, can be obtained by the use of dense hydroxyapatite ceramics and by the implementation of the steps a) and b) of the method according to the invention.

Evidence pertaining to secondary considerations must be taken into account whenever present. M.P.E.P. § 2145, citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

Proper consideration of the secondary considerations that are present here (i.e., the unexpected results explained above) supports a conclusion of nonobviousness over the art of record.

C. Troczynsky Teaches Away

One skilled in the art in view of the teaching of Troczynsky et al would not have been motivated to use hydroxyapatite ceramic for cellular transfection prolonged in time. On the contrary, the teaching of Troczynsky et al, which discloses that ceramic of hydroxyapatite wherein molecules are adsorbed onto, allows fast liberation of these molecules, would have discouraged one skilled in the art.

Troczynsky suggests (in particular by example 3) to use particles of the type BM-HA and SG-HA, wherein DNA is encapsulated, to obtain cellular transfection prolonged in time. In fact, the degradation of these particles, which takes time, is required to release DNA. However, such particles have the drawbacks to require their degradation to release DNA; this can modify the extracellular medium, be toxic and can lead to cellular death, in particular in closed medium like culture cellular medium.

Further, Troczynsky describes (page 4, lines 25-30) hydroxyapatite ceramic, wherein drugs are adsorbed onto. Troczynsky specifies that hydroxyapatite ceramic has the drawback to release drugs over a short period of time. Troczynsky thus emphasizes the undesirability of this approach, thereby discouraging a skilled artisan and teaching away from the present invention as defined in the claims as amended.

D. Dependent Claims Are Nonobvious

If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. M.P.E.P. § 2143.03, quoting *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicants have established nonobviousness of claim 1 as amended, as explained above. Accordingly, the dependent claims, which depend directly or indirectly from claim 1, are also nonobvious.

Conclusion

For all above stated reasons, the amendments contained herein clearly establish patentability over Troczynsky. Thus, entry of the amendment would place the present application in condition for allowance. Moreover, this Amendment raises no new issues and would require no further search. Accordingly, the amendment is suitable for entry.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to

Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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